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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,300	08/21/2001	Todd Lewis Talarico	35780/233666 (5780-5)	8297

826 7590 07/15/2005

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,300	TALARICO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Applicants' Response

Applicants' Response

1) Acknowledgment is made of Applicants' response filed 06/13/05 in response to the Office Action mailed 03/10/05.

Finality Withdrawn

2) The finality of the previous Office Action mailed 03/10/05 is hereby withdrawn in light of the explanation/discussion set forth below.

Applicants' arguments filed 06/13/04, with respect to the rejection(s) of instant claim(s) under 35 U.S.C. § 102 and § 103 have been fully considered and are persuasive as explained in paragraph 6 below. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is set forth in view of newly found prior art reference of Greenwald *et al. Bioconjugate Chem.* 7: 638-641, 1996, which was neither identified by Applicants on an IDS in the instant application, nor by the Office previously.

Status of Claims

3) No claims have been amended via the papers filed 06/13/05.

Claims 12-19 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

6) The rejection of claims 12, 13, 14, 15, 16, 18 and 19 made in paragraph 9 of the Office Action mailed 11/16/04 and made/maintained in paragraph 7 of the Office Action mailed 03/10/05 under 35 U.S.C. § 102(b) as being anticipated by Nho *et al.* (US 5,234,903 - Applicants' IDS), is

withdrawn mainly in light of Applicants' argument that the filtered ethanolic solution is of the ω-azido PEG intermediate as opposed to the activated ω-amino-PEG.

7) The rejection of claim 17 made in paragraph 11 of the Office Action mailed 11/16/04 and made/maintained in paragraph 8 of the Office Action mailed 03/10/05 under 35 U.S.C. § 103(a) as being unpatentable over Nho *et al.* (US 5,234,903 - Applicants' IDS) as applied to claim 16 above, is withdrawn for reasons explained *supra*.

Rejection(s) under 35 U.S.C. § 102

8) Claim 12 is rejected under 35 U.S.C. § 102(b) as being anticipated by Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996).

It is noted that the term 'contaminants' is defined in the instant specification as referring to compounds including, but not limited to, bioburden, endotoxin and particulates. The term bioburden is defined as referring to organisms such as bacteria that may be present in the dissolved activated PEG. See lines 7-12 on page 6 of the instant specification.

Greenwald *et al.* taught a method of modifying a hemoglobin with a stable activated T-PEG dissolved in water and buffer using 'a solution addition procedure' (see first six lines under 'Discussion' on page 640). Greenwald *et al.* taught a method of preparing a PEG-modified hemoglobin solution by conjugating, under mild conditions, an exceptionally stable activated PEG derivative, T-PEG, in solution with a hemoglobin solution. Greenwald *et al.* expressly taught that T-PEG offers two important advantages over other activated PEGs, such as, SC-PEG and other succinimidyl-activated linkers: (a) T-PEG is relatively stable in aqueous solutions making it possible liquid-liquid additions rather than the typical solid addition of activated PEG to protein solutions; and (b) reaction occurs without concomitant change in pH, thus enabling pH sensitive proteins to be conjugated without difficulty (see page 641, left column; title; and page 638). Greenwald's method includes dissolving the significantly more stable T-PEG in water prior to adding it to protein. Greenwald's T-PEG in solution is subject to filtration (see page 639, right column). The T-PEG is dissolved in acetonitrile and subject to size exclusion HPLC (see page 640). The chemically modified hemoglobin solution is produced by combining the activated stable T-PEG dissolved in a buffer solution with a solution of hemoglobin (see page 640, left column). Greenwald's method anticipates the instantly claimed method. The open-ended claim language

'comprising' in claim 12 does not exclude additional steps unrecited in the claim(s). See M.P.E.P 2111.03 [R-1]. Therefore, the step of lyophilizing T-PEG dissolved in acetonitrile following the filtration step is permitted before combining the buffer solution containing T-PEG with a hemoglobin solution. That the prior art step of filtration includes the use of a filter and necessarily reduces the levels of contaminants substantially, including particulates, bioburden, or endotoxin, is inherent from the teachings of Greenwald *et al.*

Claim 12 is anticipated by Greenwald *et al.*

Rejection(s) under 35 U.S.C. § 103

9) Claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996) as applied to claim 12 above, and further in view of Talarico *et al.* (*Biochim. Biophys. Acta* 1476: 53-65, 03 January 2000, already of record).

The teachings of Greenwald *et al.* are explained above which do not disclose activated PEG to be POE.

However, the use of POE in the modification of hemoglobin was well known in the art at the time of the invention. For example, Talarico *et al.* (2000) taught the use of polyoxyethylene or POE in the derivatization of pyridoxalated stroma-free haemoglobin (PHP) to increase the hydrodynamic volume or apparent molecular weight of the PHP (see second full paragraph on page 54). Talarico *et al.* taught the advantage of using POE by stating that a unique aspect of using POE for modification is that, unlike its mono-methoxy PEG relatives, POE is bifunctional (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Greenwald's PEG with Talarico's POE to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit providing advantageously a bifunctional POE in Greenwald's method for the purpose of increasing the hydrodynamic volume or apparent molecular weight of the PHP as taught by Talarico *et al.* (2000).

Claim 13 is *prima facie* obvious over the prior art of record.

10) Claim 14 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996) as modified by Talarico *et al.* (*Biochim. Biophys. Acta* 1476: 53-65, 03 January 2000, already of record) as applied to claim 13 above, and further in view

of Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993, already of record) or Blume *et al.* (*Biochimica et Biophysica Acta* 1029: 91-97, 1990) and Maraganore *et al.* (US 5,256,559).

The teachings of Greenwald *et al.* as modified by Talarico *et al.* are explained above which do not disclose the solvent to be ethanol, methanol or acetonitrile.

However, it was routine in the art at the time of the invention to dissolve an activated PEG in an organic solvent such as ethanol, acetonitrile or methanol. For instance, Woghiren *et al.* taught a method of preparing a chemically modified protein solution which involves the step of activating PEG into a stable reagent. In particular, Woghiren *et al.* taught dissolving the activated PEG in a solvent, such as, methanol solution (see abstract; page 314, left column; and 'Experimental Procedures', especially on page 315).

Blume *et al.* taught a PEGylation process wherein the activated PEG was dissolved in methanol/chloroform before combining it with a molecule to be PEGylated, which was also dissolved in methanol/chloroform (see paragraph bridging left and right columns on page 92).

Maraganore *et al.* taught that during the coupling of a peptide to an activated derivative of PEG using conventional techniques to increase the biological half-life of the peptide, the attachment of the peptide with the activated PEG can be effected in an organic solvent or a buffered solution (see first full paragraph in column 9).

Given the routine use of an organic solvent, such as, ethanol or methanol, in dissolving an activated PEG as taught by Woghiren *et al.*, Maraganore *et al.* or Blume *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace with or to add to the buffer solution in Greenwald's method as modified by Talarico *et al.* Woghiren's or Blume's methanol solution to produce the instant invention with a reasonable expectation of success. Since both activated PEG and the molecule to be PEGylated have been previously dissolved in the art in methanol before being combined in solution as taught by Maraganore *et al.*, one of skill in the art would have been motivated to produce the instant invention for the expected benefit providing an art-known solution alternative to Greenwald's buffer solution. Substitution of one solution with another alternative art-known solution or addition of methanol to an art-existing buffer solution is well within the realm of routine experimentation and would have been obvious to one of ordinary skill in the art.

Claim 14 is *prima facie* obvious over the prior art of record.

11) Claims 15 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996) as modified by Talarico *et al.* (*Biochim. Biophys. Acta* 1476: 53-65, 03 January 2000), Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993, already of record) or Blume *et al.* (*Biochimica et Biophysica Acta* 1029: 91-97, 1990) and Maraganore *et al.* (US 5,256,559) as applied to claim 14 above, and further in view of Shorr (US 5,900,402).

The teachings of Greenwald *et al.* as modified by Talarico *et al.*, Woghiren *et al.* or Blume *et al.* and Maraganore *et al.* are explained above which do not disclose that the filtration was through at least one filter that substantially reduces the levels of endotoxin contaminants as recited claims 15 and 16.

The use of membrane filters, such as, Sartorius Q membranes, for the removal of negatively charged endotoxins from an activated PEG-containing solution was well known in the art at the time of the invention. For instance, Shorr taught the use of Sartorius Q membranes for the removal of negatively charged endotoxins, or microfiltration using a 22μ filter to filter an activated PEG-containing solution which reduced the endotoxin levels to less than 2 Eu/ml (see Example 1). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include Shorr's Sartorius Q membrane or 22μ filter in the filtration step of Greenwald's method to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of advantageously removing or reducing the levels of negatively charged endotoxins to a level indicated above as taught by Shorr.

Claims 15 and 16 are *prima facie* obvious over the prior art of record.

12) Claims 17 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996) as modified by Talarico *et al.* (*Biochim. Biophys. Acta* 1476: 53-65, 03 January 2000, already of record), Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993, already of record) or Blume *et al.* (*Biochimica et Biophysica Acta* 1029: 91-97, 1990), Maraganore *et al.* (US 5,256,559) and Shorr (US 5,900,402) as applied to claim 16 above, and further in view of Nho *et al.* (US 5,234,903, already of record).

The teachings of Greenwald *et al.* as modified by Talarico *et al.*, Woghiren *et al.* or Blume *et al.*, Maraganore *et al.* and Shorr are explained above which do not expressly disclose that the filter used was a 0.2 micron nylon filter.

However, the use of nylon filters for filter sterilization of PEG-containing solutions was known in the art at the time of the invention. For instance, Nho *et al.* expressly taught the use of a 0.2 micron Zetapor membrane (i.e., nylon) filter for filter sterilization of the PEG-containing solution. See sections 6.1.5, 6.2, 10.1.5, 10.2.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the Sartorius Q membrane or the 22μ filter in Greenwald's method as modified by Talarico *et al.*, Woghiren *et al.* or Blume *et al.*, Maraganore *et al.* and Shorr with an alternative art-known filter such as Nho's 0.2 μ Zetapor membrane nylon filter to produce the instant invention with a reasonable expectation of success. Substitution of one filter with another alternative art-known filter for the purpose of sterilization is well within the realm of routine experimentation, would have been obvious to one of skill in the art, and would have brought about similar results.

Claims 17 and 18 are *prima facie* obvious over the prior art of record.

13) Claim 19 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Greenwald *et al.* (*Bioconjugate Chem.* 7: 638-641, 1996) as modified by Talarico *et al.* (*Biochim. Biophys. Acta* 1476: 53-65, 03 January 2000, already of record), Woghiren *et al.* (*Bioconj. Chem.* 4: 314-318, 1993, already of record) or Blume *et al.* (*Biochimica et Biophysica Acta* 1029: 91-97, 1990), Maraganore *et al.* (US 5,256,559), Shorr (US 5,900,402) and Nho *et al.* (US 5,234,903 - Applicants' IDS) as applied to claim 18 above.

The teachings of Greenwald *et al.* as modified by Talarico *et al.*, Woghiren *et al.* or Blume *et al.*, Maraganore *et al.*, Shorr and Nho *et al.* are explained above which do not expressly disclose that the filtering and combining steps are aseptically joined.

However, in addition to teaching the use of nylon filters for filter 'sterilization' of PEG-containing solutions using a 0.2 μ Zetapor nylon membrane, Nho *et al.* also taught accomplishing the method steps involved in preparing a chemically modified pyridoxylated stroma-free hemoglobin solution under sterilizing conditions (i.e., aseptically). See sections 5.1.1.1; 5.1.4;

6.1.5; 6.2; 10.1.5; and 10.2.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the combining step in Greenwald's method as modified by Talarico *et al.*, Woghiren *et al.* or Blume *et al.*, Maraganore *et al.*, Shorr and Nho *et al.* under sterilizing conditions as taught by Nho *et al.* to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of ensuring sterility at every step during the production of the of the activated POE-pyridoxylated Hb solution since a high degree of sterility is ideally desired in the art for a product that is meant for *in vivo* administration.

Claim 19 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

14) The prior art made of record and not relied upon currently in any of the rejections is considered pertinent to Applicants' disclosure.

- At the time of the instant invention, it was routine to dissolve a PEG polymer in an organic solvent during its activation. For example, see lines 21-28 in column 4 of Saifer *et al.* (US 5,468,478).

- Abuchowski *et al.* (*J. Biol. Chem.* 252: 3578-3581, 1977) taught the step of filtering, once or more than once, a solution of activated PEG, methoxypolyethylene glycol, to remove residual reagents, before using it for conjugation to a protein (see paragraph bridging pages 3578 and 3579).

- Blume *et al.* (*Biochimica et Biophysica Acta* 1029: 91-97, 1990) taught a PEGylation process wherein an activated PEG dissolved in methanol/chloroform was combined with a solution of distearoylphosphatidylethanolamine dissolved in methanol/chloroform using the method of Abuchowski *et al.* (*J. Biol. Chem.* 252: 3578-3581, 1977). See paragraph bridging left and right columns on page 92.

Remarks

15) Claims 12-19 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions

24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

17) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER